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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/828,316
Filing Date: April 21, 2004
Appellant(s): GERTZMAN ET AL.

John S. Hale
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 05/04/2006 appealing from the Office action mailed 08/03/05**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. Appellant amendments to the claims have been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 7, 8 and 21-28 are rejected as unpatentable under 35 U.S.C. 103(a) over Boyce et al (US 6, 294, 187, filed February 23, 1999) in view of Breitbart et al (US 5, 700, 289) further in view of Sander et al (US 5, 356, 629).

Claims 2,7,8,10 and 21-25 are directed toward bone composition comprising osteoinductive bone particles in aqueous medium in the form of a hydrogel comprising chitosan and sodium alginate; the composition contains growth factor additives such as transforming growth factor and cellular materials (living cells, cell elements, fibroblasts, epithelial cells etc, The bone particles are added at 5-50% concentration (w/w); the molecular weight of the hydrogel ingredient is 10,000 to 300,000; the endothelial cells are added to give 10^5 cells/ml and the pH of the suspension is near physiological pH. Claims 2, 7,8 and 10 are directed toward the bone particle size (100-850 microns), the concentration of bone particles and the number of cells present in the carrier aqueous solution.

Claims 26-28 are directed toward a bone compositions taken from allograft, cortical, corticalcancellous, cancellous, autologuous and xenograft bone wherein particles are

allograft cortical bone ranging from 100-850 microns, these compositions include demineralized chips, non demineralized chips of sizes from 0.1mm to 1.0 cm with a concentration of about 5% to about 25%.

Boyce et al. (Patent t 1 87) disclose osteoimplant composition comprising bone particles in physiological saline (col. 2, lines 45-50, col. 3, line 20 and col. 11, lines 20-25) wherein the composition exhibits biological properties as in applicant's instant claims (e.g. osteoconductivity and/or osteoinductivity col. 7, lines 1-10). According to Boyce, the bone particles can optionally be sieved to produce particles of a specific size (col. 4, lines 50-55 and continuing to col. 5, lines 1-25) and further discloses bone particle content in terms of the wt% of the particles in the composition (col. 5, lines 30-35, col. 6, lines 15-25 and col. 8, lines 50-55). Patent '187 also discloses the use of chitosan and hydrogels (col. 8, lines 15 and col. 1, lines 1-10). Patent 'I 87 also discloses the use of bioactive substances in the bone repair composition (e.g. transforming growth factor; col. 9, lines 50-60). Patent t 187 does not teach the use of alginate and other sources of cells in the composition.

Beside the demineralized bone particles that patent '187 also disclosed, it also teaches bone particles in the preparation of the bone particle-containing composition can be obtained from cortical, cancellous and/or corticocancellous bone which may be of autogenous, allogenic and/or xenogeneic origin. Preferably, the bone particles are obtained from cortical bone of allogenic origin (col. 4, lines 42-45). The bone particles in the composition can be powdered bone particles possessing a wide range of particle sizes ranging from relatively fine powders to coarse grains and even larger chips.

Powdered bone particles can range in average particle size from about 0.05 to about 1.2, considering using the word "about" in the prior art and in the claims of the current application the range is almost the same (col. 4, lines 56-59).

Breitbart et al (Patent '289) supplies the deficiencies of Patent t 'I87 in that Breitbart et al disclose bone repair composition comprising cells such as stem cells, chondrocytes and mesenchyma cells (col. 2, lines 45-60, col. 4, lines 25-30 and col. 14, lines 60). Additionally, Patent '289 discloses the use of both alginate and chitosan as the hydrogel forming ingredients (col. 6, lines 35-40, col. 10, lines 5- 10, lines 40-45 and col. 11, lines 35-40).

Sander et al (Patent '629) discloses a composition suitable for bone repair comprising biocompatible particles dispersed in a matrix that can be implanted into defective bone tissue (abstract, col. 2, lines 35-40, col. 3, lines 50-55 and col. 5, lines 35-40). Patent '629 discloses the use of drugs and other substances that can induce bone growth in the composition (col. 4, lines 55-654) continuing to col. 5, lines 1-15). More significantly, Patent '629 discloses that the biocompatible particles of any size may be used in the composition and that matrix material can be conveniently comminuted to the appropriate particle size of mixing (col. 4, lines 30-39 and col. 35-40).

One of ordinary skill in the art would be motivated to prepare a composition comprising bone particles and bioactive agents having osteoinductive properties such as growth factors to form a bone cement composition as disclosed in the prior art cited. By combining the methods disclosed in the prior art cited, one of ordinary skill would

expect to obtain a composition that can be molded and implanted into a bone defective site in order to induce bone growth and repair while preventing or mitigating the possibility of infection at the injured site due to the antibiotic action of the drugs incorporated into the composition, Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

The following prior art reference is cited for the record only as pertinent to applicant's claims but is not relied upon for the current rejection in the office action:

Wolfinbarger et al (US 5, 531, 79 1). The reference teaches bone composition in gel or hydrogel form comprising bone particles and optional components such as growth factors and osteoblasts (abstract, col. 4, lines 1-30, lines 50-604 col. 5, lines 40-45, col. 7, lines 20-25 and col. 9, lines 20-35). The reference is not applied because it does not teach the use of alginate or chitosan in the composition.

** Upon entrance of the Applicant's amendments filed on 12/05/2005, claims 2,7,8, 21-28 are pending in the application.

(10) Response to Argument

Appellant argues that the claims should be divided into. However Examiner find no obligation for grouping the claims since they all recite one invention. According to the Appeal Brief filed, the grouping of the arguments makes it too long while very repetitive. Accordingly, the Examiner's response to the arguments will be addressed to the list of claims as one group.

Appellant's arguments filed 05/04/2006 have been fully considered but they are not persuasive. Appellant argues that:

The **Boyce '187** teaches a shaped hardened load bearing osteoimplant bone structure formed of compressed bone particles and not powdered demineralized bone particles mixed in a carrier of sodium alginate an/or chitosan forming a formable putty composition. Compressive forces typically ranging from about 2,500 to 60,000 psi are applied to bone particles in press-mold to produce a hard chalk-like material. (Col. 11, lines 65-66). The material can then be easily shaped or machined into any of a wide variety of configurations. As noted in the '187 patent the resulting osteoimplant can assume a determined or regular form or configuration such as a sheet, plate, disk, cone, pin, screw, tube, tooth, tooth root, bone or portion of bone, wedge or portion of wedge, cylinder, threaded cylinder (dowel) to name but a few. Of course, the osteoimplant can be machined or shaped by any suitable mechanical shaping means. In the preferred embodiment, the osteoimplant possesses the configuration of a threaded cylinder (dowel) (Col. 14, lines 6-16). It is also noted that the osteoimplant is applied at a bone repair site which requires mechanical support (Col. 14, lines 21- 25) and can be implanted using any suitable affixation means, e.g., sutures, staples, bioadhesive, and the like. (Col. 14, lines 49-51).

The Boyce et al '187 compressed bone structure is formed by applying compressive force of at least about 1000 psi, has a bulk density greater than about 0.7 cm^3 and a wet composite strength substantially exceeding 3MPa to form a hardened mass. The bone particles which are used in the hardened structure are formed by

milling whole bone to produce fibers, chipping whole bone, cutting whole bone, fracturing whole bone in liquid nitrogen or otherwise disintegrating the bone tissue. The bone particles range in average particle size from about 0.05 to about 1.2 cm in size and possess an average median length to median thickness of from about 1:1 to about 3:1. Alternatively or in combination with the previously mentioned bone particles, bone particles, which are generally characterized as elongate and possessing relative high median length to median thickness ratios are utilized. The elongate particles are obtained by milling or shaving the surface of an entire bone with at least 60%, preferably 90% of the bone particles being elongated. These elongated particles possess a medium length from about 2 to 200 mm and preferably from about 10 to about 100mm. These elongate bone particles can possess a median length to median thickness ratio of at least about 50:1 up to about 500:1 or more. In Boyce et al '187, preferably, at least about 60 weight percent, more preferably at least about 75 weight percent and most preferably at least about 90 weight percent of the bone particles utilized in the preparation of the bone particle-containing composition are elongate. It is noted that elongate bone particles provide an osteoimplant possessing particularly good compressive strength. It can thus be seen that the characterization of the Examiner that the sizes of the bone particles used in Boyce et al '187 correspond to that of the present invention is not correct. Furthermore there is no way that Boyce et al. '187 could be characterized as formable. The composition fabricated in accordance with the Boyce et al disclosure more preferably has a bone content ranging from about 50-95% by weight of the entire composition.

As noted in the Examples of Boyce et al '187, the bone particles were mixed different solutions such as glycerol (Examples 1, 12), cross linked with formalin (Examples 2 and 3), saline (Example 4), ethanol and ethyl cellulose (Examples 5, 6, 7, 8), and water (Examples 9, 10, 11). There is no teaching in the examples of the carrier of the present invention, the bone particle range, the weight of the carrier and range of the same, viscosity or any concentration of cellular material (Boyce et al '187 being a solid and having no viscosity). Appellant would point out that the use of hydrogels is disclosed only as a thickener when water and/or glycerol are used as the wetting agent for forming the slurry. These hydrogels are used to suspend and keep the bone particles separate during the application of the compression forces to form the solid structure and do not act as a carrier for the bone particles possessing particularly good compressive strength.

1. To respond to this argument, '187 is teaching bone particles in the composition which can be powdered bone particles possessing a wide range of particle sizes ranging from relatively fine powders to coarse grains and even larger chips. Thus, e.g., powdered bone particles can range in average particle size from about 0.05 to about 1.2 cm (col.4, lines 55-63), for controlling the size of the particles, '187 teaches that particles can optionally be sieved to produce particles of a specific size (col.4, line 51,52). In response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which appellant relies (i.e., bone powder) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into

the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims of the present application does not recite a powdered bone particles.

Using milling in '187 shows that the elongated particles cannot be the only kind of particles in the invention, milling is a final step in the production of bulk substances to reduce the particle size distribution of the material. Rigorous milling is used to reduce the primary particle size in an effort to improve formulation, homogeneity or bioavailability of an amorphous substance (*Harry G. Brittain, David J. Grant, Keith Guillory, and Polymorphism in Pharmaceutical Solids,* New York: Marcel Dekker Inc., 1999 Pages: 334, 212, 213). In addition, in the claims of the instant application, appellant did not specify the shape of the particles. Appellant also failed to show criticality or unexpected results in the specific size of the instant application particles. With regard to the "formable bone" of the instant application, it has not been given patentable weight because the recitation occurs in the preamble. Also traversing the reference for the compressive force of at least about 1000 psi of '187 is not crucial since it is a step of the method of preparation and it does not have a corresponding step recited in the instant application to be compared to.

Appellant also argues that chitosan is only noted as an adhesive for the demineralized bone particles and is incidentally found as one of a 30+ line list of suitable adhesives or as a thickener to preclude premature bone particle separation and improve suspension.

To respond to this argument Chitosan is being disclosed in '187 invention as an adhesive or a thickener, a compound and its properties are not separable; the prior art

clearly administers chitosan in the composition that is used for same patients. It is not necessarily that the prior art recognizes each and every advantage that a compound can accrue from the use of the particular ingredient, (see claims 6, 51), and (col. 8, lines 13-40, col. 10, lines 58-57).

Sander et al '629, Appellant argues that:

'629 does not disclose demineralized bone used as the nonbioadbsorbable material and demineralized bone is used as an additive in the nature of a bioactive agent.

The Examiner's inference that the '629 patent teaches that the composition can comprise living cells such as erythrocytes, leucocytes and endothelial cells and that the pH of the composition is approximately 6.8-7.4 is not based on the teachings of the '629 patent and is a hind site supposition.

Sander et a1. '629 does not teach or obviate the present invention alone or combined with the other cited references. Use of (1) demineralized bone material as the nonbioabsorbable material and as a major component of the composition or (2) an equivalent biocompatible material weight (3) a phosphate buffer to neutralize the composition and (4) the addition of cellular material at a concentration of 10^5 to 10^8 per cc of the carrier is not taught or disclosed. Furthermore Sander et al is not osteogenic relying on antigenic response.

**Appellant adds in the after-final and appeal brief remarks that Sander does not disclose carrier of chitosan and molecular weight of the carrier which is the same as the molecular weight of the inventive carrier.

To respond to these arguments, '629 discloses that the bioactive substance can also be an osteogenic agent, which stimulates or accelerates generation of bone upon implantation into a bone defect site. Such osteogenic agent includes osteoinductive protein, demineralized bone powder in addition to morselized cancellous bone, aspirated bone marrow, and other autogenous bone sources (col. 5 lines 11-17). It is the position of the examiner to remind appellant of the fact that it is not necessarily that the prior art recognizes each and every advantage that a compound can accrue from the use of the particular ingredient.

Upon reviewing office action mailed by the examiner on 10/15/2004, inference stated by appellant is not found, on the other hand, examiner infers that '629 discloses using drugs and other substances that can induce bone growth in the composition (col. 4, lines 55-65).

** Regarding the chitosan and the molecular weight addressed by Appellant in the after final remarks, the molecular weight of the instant application is within the matrix molecular weight used by '629 and Boyce'187 disclosed the chitosan.

Breithart et al '289 Appellant argues that:

Art discloses cells, chondrocytes and mesenchmal cells as prior art showing the use of autologous cells and chondrocytes attaching to hydroxyapatite, and discloses the use of periosteum, which consists of multipotent mesodermal cells. Claim refer to periosteum cells seeded in biocompatible matrix.

The disclosure of alginate and chitosan in a large laundry list of potential natural and synthetic polymers, which can be used to form a fibrous or sponge-like matrix for the seeding of cell, includes alginate.

The matrix is solid as it is preferably made of hydroxyapatite, tricalcium phosphate, sterilized bone or metal alloy.

In response to the above argument, the examiner position is to confirm that:

Appellant argument regarding the citation of used cells in the prior art is considered acceptable, it was cited only from the prior art as the background of the invention, however, the mesenchymal stem cells are disclosed in example 1. In addition, the periosteal cells that were used in the invention are known in histology to be a connective tissue of the periosteum, the periosteum has two layers: an outer fibrous layer with typical fibroblasts, and an inner cellular layer, which contains osteoprogenitor cells. The osteoprogenitor cells in this location are called periosteal cells. They are capable of giving rise to osteoblasts, which secrete the extracellular matrix of bone.

The disclosure of chitosan and alginate where cited in a long laundry list does not cancel the fact that the prior art discloses the two components before the instant application, furthermore the art discloses the examples of materials which can be used to form a hydrogel include polysaccharides such as alginate (col. 10, lines 12-14). Though chitosan is still one compound disclosed in the laundry list, it makes no big effect on the rejection because it was disclosed clearly in the primary art '187.

The appellant statement of a solid matrix is not conclusive as he describes this matrix as one of the preferred and not all what the art discloses. The hydrogel is

disclosed in the art as follows: (col. 3, line 34, col. 6, line 1-2, col. 7, line 59, line 55, 56, col. 10, line 8, col. 11, line 19,15, 21, 25, 28, claims 4, 12).

In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Examiner would like to address that the Appellant should consider the teaching of the primary art, which is Boyce et al. (US 6, 294, 187), combined with the teachings of the two secondary arts, which are Breitbart et al. (US 5, 700, 289) and Sander et al (US 5, 356, 629).

In brief, art '187 (Boyce et al., the primary art) teaches: (1) osteoimplant composition comprising bone particles in (2) physiological saline (3) the composition exhibits osteoconductivity and/or osteoinductivity (4) the particles of the composition can be produced to a specific size (5) bone particle content of the composition wt% is disclosed in (col. 5, lines 30-35, col. 6, lines 15-25 and col. 8, lines 50-55) (6) chitosan and hydrogel (7) bioactive substances in the bone repair composition.

It does not teach (1) the use of alginate and (2) other sources of cells in the composition.

Art '289 (Breitbart et al, secondary art) teaches (1) the use of alginate and chitosan (2) cells such as mesenchymal stem cells, chondrocytes and mesenchyma cells as the ingredients forming (3) hydrogel.

Art '629 (Sander et al. secondary art) teaches (1) composition for bone repair comprising particles dispersed in a matrix (2) can be implanted into defective bone tissue (3) discloses the use of drugs and other substances that can induce bone growth (4) biocompatible particles of any size can be used in the composition and (5) matrix material can be conveniently comminuted to the appropriate particle size.

The three references are combined to show obviousness of the instant claims as expanding the knowledge of '187 by adding alginate from '289 and sources of cells from '629. According to the final office action, one of ordinary skill in the art would be motivated to prepare a composition comprising bone particles and bioactive agents having osteoinductive properties such as growth factors to form a bone cement composition by combining the prior art cited, one of ordinary skill would expect to obtain a composition that can be molded and implanted into a bone defective site in order to induce bone growth and repair while preventing or mitigating the possibility of infection at the injured site due to the antibiotic action of the drugs incorporated into the composition, Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Nabila Ebrahim

Nabila

Art Unit 1618

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